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Congeners of Troeger's base as chiral ligands

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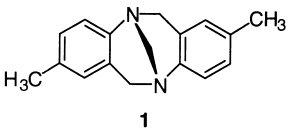
Abstract

(*S*)-(+)-Troeger's base can be deprotonated and alkylated without loss of stereochemical integrity. An examination of the ability of Troeger's base and several derivatives prepared in this fashion to effect asymmetric induction in the addition of diethylzinc to aromatic aldehydes was conducted. Enantiomeric excesses as high as 86% were achieved, providing evidence that Troeger's base represents a chiral framework which can be modified to produce ligands for catalytic asymmetric synthesis. © 2000 Published by Elsevier Science Ltd.

Troeger's base **1** is an interesting rigid, polycyclic diamine which has a long and venerable history and has more recently received attention as a template around which to construct unique architectures for studies of molecular recognition and inclusion.[1,2] The synthesis of Troeger's base in enantiomerically pure form has been achieved by an asymmetric transformation and other template-based approaches appear to be viable as well.[3,4] We recently reported that Troeger's base could be metalated at the benzylic methylene position and subsequently quenched with a variety of electrophiles, making heretofore unknown analogues of Troeger's base available for study.[5]



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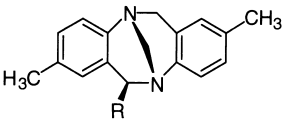

2: R = -CH_2OH
3: R = -CPh_2OH
4: R = -CH_2CPh_2OH
5: R = -$CH_2OCH_2CPh_2OH$

Despite it chirality, little has been done to exploit Troeger's base as a chiral ligand. Metal complexes of Troeger's base have been reported and their use as catalysts in the hydrosilylation of alkynes documented.[6,7] To the best of our knowledge, only one report has appeared which

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documents the use of Troeger's base as a chiral ligand for asymmetric catalysis.[8] In this paper, we report the first example of derivatives of Troeger's base as chiral ligands.

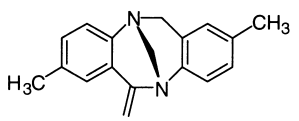
While it appears clear that the development of new ligands for the enantioselective addition of diethylzinc is not a pressing issue, the process serves as a useful testing ground for new ligand development.[9,10] We thus chose to study Troeger's base and several congeners in this context. Several questions needed to be answered in the course of this work. First, would Troeger's base itself serve as a useful ligand for the reaction? Could enantiomerically pure Troeger's base be successfully taken through our alkylation chemistry without loss of stereochemical integrity? Finally, could enantioselectivities be improved by ligand modification, if necessary?

Commercially available (*S*)-(+) Troeger's base was first examined as a ligand.[11] The standard reaction conditions for all of our work involved treating a 0.2 M solution of aldehyde in toluene at room temperature with 2.2 equivalents of diethylzinc in the presence of 5 mol% of ligand. The reactions were worked up after 48 hours. These reactions generally did not go to completion. The results with Troeger's base as a ligand are shown in Table 1. Not too surprisingly, the enantioselectivity was poor.[12] It is interesting to note that the highest ee was achieved with *o*-bromobenzaldehyde (Table 1, entry 4), especially since *ortho*-substituted aldehydes tend to give low ee's relative to their positional isomers. These data provided a baseline with which to judge the quality of results with other ligands in diethylzinc additions.

Table 1
Asymmetric addition of Et_2Zn to benzaldehydes in the presence of **1**

Entry	Aldehyde	Yield (%)	ee (%)	Config.
1	PhCHO	48	13	R
2	pClPhCHO	74	17	R
3	pOMePhCHO	56	7	R
4	oBrPhCHO	76	22	R
5	pBrPhCHO	46	10	R

We initially decided to prepare ligands **2**–**5**. Ligands **2**–**4** were prepared using chemistry we have already described.[5] For example, treatment of a THF solution of **1** with BF_3–Et_2O at 0°C, followed by treatment with *n*-BuLi, gave an intermediate which was quenched with BOC anhydride. Reduction with lithium aluminum hydride gave **2** in 59% overall yield from **1** (Scheme 1). Ligands **3** and **4** were prepared directly from **1** in yields of 67 and 73%, respectively.[13] It should be noted that in the preparation of **4**, *t*-BuLi was used to directly metalate **1** and the use of a Lewis acid was not necessary. Attempts to prepare **5** by the alkylation of **1** with 1,1-diphenylethylene oxide resulted in the formation of a compound to which we have tentatively assigned the structure **6** in approximately 32% yield. It has not yet been possible to suppress the apparent elimination process leading to **6**. Despite this setback, we viewed the selection of ligands available as suitable to our needs.



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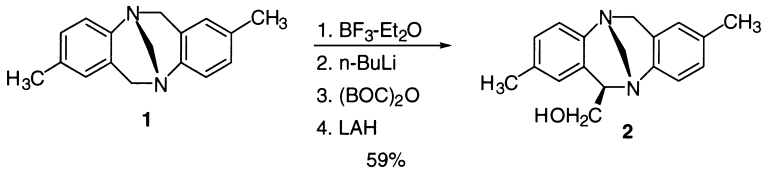


Scheme 1.

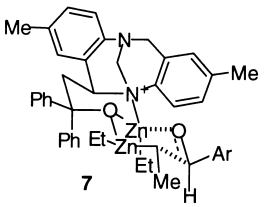
Data for the addition of diethylzinc to benzaldehydes using **2**–**4** are summarized in Table 2. These reactions did not go to completion and no attempt was made to correct the yields for recovered starting material. Ligand **2** afforded alkylation products with only poor enantiomeric excesses (Table 2, entries 1–5). With one exception, increasing steric bulk at the carbinol carbon improved the situation somewhat as demonstrated with ligand **3** (Table 2, entries 6–10). It is interesting to note that, in contrast to Troeger's base itself, both of these ligands preferentially produced the *S* enantiomer of the product carbinols. Since ligands **2** and **3** have two potentially catalytically active sites, which lead to opposite enantiomeric preferences, it is of interest to determine the relative rate at which each site leads to product. We have examined this question in a very qualitative way.

Table 2
Asymmetic addition of Et_2Zn to aldehydes in the presence of **2**–**4**

Entry	Aldehyde	Ligand	Yield (%)	ee (%)	Config.
1	PhCHO	**2**	46	34	S
2	pClPhCHO	**2**	76	36	S
3	pOMePhCHO	**2**	50	38	S
4	oBrPhCHO	**2**	38	20	S
5	pBrPhCHO	**2**	61	35	S
6	PhCHO	**3**	56	52	S
7	pClPhCHO	**3**	85	56	S
8	pOMePhCHO	**3**	36	53	S
9	oBrPhCHO	**3**	43	0	S
10	pBrPhCHO	**3**	55	56	S
11	PhCHO	**6**	63	83	R
12	pClPhCHO	**6**	66	84	R
13	pOMePhCHO	**6**	58	81	R
14	oBrPhCHO	**6**	37	67	R
15	pBrPhCHO	**6**	79	86	R

The reaction of benzaldehyde and diethylzinc was conducted with racemic **1** and **3** and the approximate rate of conversion of the aldehyde to product monitored for each process. The data indicated that the reaction with **3** as catalyst was only about four times faster than when using **1**. This suggests that the aminoalcohol catalytic site in **3** is actually more enantioselective than the data indicate.

Interestingly, ligand **4** produces a fairly high enantiomeric excess of the *R* enantiomers of the product alcohols. A model for delivery of the ethyl group to the aldehyde to account for the stereochemical outcome of this process is shown in structure **7**. Though no data are presently available, it may also be the case that the amine site in the ligand leads to lower enantioselectivities than would be theoretically possible.



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In summary, we have demonstrated that the stereochemical integrity of Troeger's base is maintained upon treatment with boron trifluoride-etherate and *n*-BuLi. We have shown that Troeger's base itself can serve, albeit poorly, as a chiral ligand for the addition of diethylzinc to benzaldehydes. Better results can be obtained with ligands **2**–**4**, demonstrating that optimization is possible. The ultimate goal of these studies is to apply ligands derived from Troeger's base to reactions which do not have as large a class of useful ligands as do diethylzinc additions. Studies of this nature will be undertaken and results will be reported in due course.

Acknowledgements

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References

1. (a) Vögtle, F. *Fascinating Molecules in Organic Chemistry*; Wiley: Chichester, 1992; pp. 237–249. (b) Bag, B. G. *Curr. Sci.* **1995**, *68*, 279. (c) Demeunynck, M.; Tatibouet, A. *Prog. Heterocycl. Chem.* **1999**, *11*, 1.
2. For an example and leading references, see: Kim, E.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192.
3. Wilen, S. H.; Qi, J. Z. *J. Org. Chem.* **1991**, *56*, 485.
4. Maitra, U.; Bag, B. G.; Rao, P.; Powell, D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2049.
5. Harmata, M.; Carter, K. W.; Jones, D. E.; Kahraman, M. *Tetrahedron Lett.* **1996**, *37*, 6267.
6. ur-Rahman, S. *J. Chem. Soc. Pak.* **1987**, *9*, 503.
7. Goldberg, Y.; Alper, H. *Tetrahedron Lett.* **1995**, *36*, 369.
8. Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1651.
9. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
10. For some recent examples, see: (a) Legrand, O.; Brunel, J.-M.; Buono, G. *Tetrahedron Lett.* **2000**, *41*, 2105. (b) Spieler, J.; Huttenloch, O.; Waldmann, H. *Eur. J. Org. Chem.* **2000**, *3*, 391.
11. The dextrorotatory (+) enantiomer is listed as 5*R*,11*R* in the Fluka catalog. However, Wilen showed that the absolute configuration of the (+) isomer is actually 5*S*,11*S*. See Ref. 3.
12. Enantioselectivity was determined by formation of the corresponding acetate and analysis on a Chiraldex B-PH column or derivatization with (*R*)-(+)-1-phenylethyl isocyanate followed by capillary GC analysis of the resulting diastereomers.
13. Data on **2**: mp 64–65°C. $[\alpha]_D^{25} = 115.2$ (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.07–7.0 (m, 2H), 6.97 (d, 2H, J = 1.0 Hz), 6.74 (d, 2H, J = 12.2 Hz), 4.68 (d, 1H, J = 16.8 Hz), 4.31 (dd, 1H, J = 1.6 Hz, 13.0 Hz), 4.16–4.07 (m, 3H), 3.92 (dt, 1H, J = 4.9 Hz, 11.1 Hz), 3.75 (d, 1H, J = 11.0 Hz), 3.26 (d, 1H, J = 11.0 Hz), 2.22 (s, 6H, br); ^{13}C

NMR ($CDCl_3$, 62.8 MHz) δ 145.8, 145.7, 133.9, 133.5, 128.8, 128.2 (2C), 127.8, 127.2, 126.8, 125.0, 124.9, 68.4, 63.5, 60.9, 58.1, 20.8 (2C). IR (KBr) 3418m (br), 1493s, 1222s, 1194m cm^{-1}. Anal. calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19. Found: C, 77.22; H, 7.00. Data on **3**: mp 100–105°C (dec). $[\alpha]_D^{25} = -270.59$ (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, 2H, J = 7.2 Hz), 7.37–7.23 (m, 8H), 7.04 (d, 1H, J = 8.1 Hz), 6.99–6.94 (m, 2H), 6.65 (s, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 4.77 (s, 1H), 4.48 (d, 1H, J = 16.7 Hz), 3.16 (d, 1H, J = 16.7 Hz), 3.65 (d, 1H, J = 13.0 Hz), 3.45 (dd, 1H, J = 0.9, 13.0 Hz), 2.21 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 146.6, 145.4, 144.4, 142.0, 134.0, 132.7, 129.0, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 127.7, 127.4, 127.3, 126.40, 125.8, 124.9, 124.3, 78.8, 77.3, 61.5, 58.3, 20.9, 20.8. IR (KBr) 3380m (br), 2950m, 1490s, 1450m, 1360m, 1217s, 1197m, cm^{-1}. Anal. calcd for $C_{30}H_{29}N_2O$: C, 83.29; H, 6.54. Found: C, 83.40; H, 6.64. Data on **4**: mp 184–185°C. $[\alpha]_D^{25} = 161.16$ (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.88 (d, 2H, J = 7.5 Hz), 7.57–7.46 (m, 5H), 7.35–7.25 (m, 4H), 7.18 (d, 1H, J = 6.3 Hz), 7.01–6.93 (m, 2H), 6.75 (s, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 6.38 (d, 1H, J = 8.2 Hz), 4.63 (d, 1H, J = 6.1 Hz), 4.57 (s, 1H, br), 4.23–4.18 (m, 2H), 4.03 (d, 1H, J = 16.7 Hz), 2.97 (dd, 1H, J = 2.7, 15.1 Hz), 2.73 (dd, 1H, J = 12.0, 15.0 Hz), 2.23 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 148.1, 146.7, 144.7, 144.4, 134.2, 133.5, 129.8, 128.6, 128.5, 128.1, 127.6, 127.3, 127.0, 126.8, 126.6, 125.3, 124.9, 124.2, 78.6, 64.5, 61.0, 58.3, 44.9, 20.9, 20.7, 14.1. IR (KBr) 3206m (br), 1497s, 1453m, 1220m, 1200m, 1063m, 1033m cm^{-1}. Anal. calcd for $C_{31}H_{30}N_2O$: C, 83.37; H, 6.77. Found: C, 83.18; H, 6.52.